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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/633,093	08/04/2000	Joel S. Greenberger	07787-004003	2079

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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/633,093	Applicant(s) GREENBERGER ET AL.	
	Examiner Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 21-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 21-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The reply to Final rejection (Paper #7), filed September 3, 2002, has been entered and as assigned as Paper #11.

The applicants correctly pointed out that claims 27 and 28 submitted in Paper #6 have not been mentioned in Paper #7. In view of such, the FINALITY IS HEREBY VACATED. Claims 1-11 and 21-30 are pending and under examination

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-10, 21, 22, 24-26, 29, and 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Anderson et al* (US 5 399 346, 3-21-1995), taken with *Greenberger et al* (EP 0 381 490 A2, 8-8-90), and *Boswell et al* (Exp. Hematol 1983) for reasons of record and the following.

In Paper #11, Applicants submitted two new exhibits, *Zaheer et al* and Mediatech Tech Information sheet, arguing that cryopreservation has a different effect on BMSCs than on other bone marrow cells, including T lymphocytes, thus, there is no basis to modify or combine the cited publications, and that there was no reasonable expectation that the combined disclosures of the publications would be a success so that the

thawed state, transfected BMSCs would have a level of expression of the exogenous gene which is at least about 77% of said predetermined value, that the combined disclosure of the publications do not teach or suggest all of the claim limitations.

The arguments and exhibits have been carefully considered but found not persuasive.

It is acknowledged that *Zaheer et al* teach the motivations and difficulties in cryopreservation of bone marrow cells, and clearly teach, "THE NUMBER OF BONE MARROW MONONUCLEAR CELLS RECOVERED AFTER CRYOPRESERVATION WAS ALWAYS LOWER THAN THAT ORIGINALLY STORED". *Zaheer et al* compare the sensitivity to freeze between hemopoietic cells and stromal cells, and teach "IT IS THE BONE MARROW STROMAL CELLS RATHER THAN THE CLONOGENIC PROGENITORS WHICH ARE SENSITIVE TO THE EFFECTS OF CRYOPRESERVATION". However, the teachings of *Zaheer et al* do not negate the feasibility of cryopreserving BMSCs, rather, they teach even though the stromal cells are more sensitive to the process of freezing and thawing, they are still alive and growing.

The Mediatech technical information sheet is a post-filling art showing different cryopreserving media for adherent or suspension cell types, they are not BMSC-specific. As shown by *Zaheer et al*, bone marrow stromal cells form layers in culture dish (section bridging pages 182 and 183), thus, they do not belong to, at least not exclusively, suspension cell type.

Assuming the cited medium is superior to the conventional one used by *Boswell and Zaheer* in cryopreserving BMSCs, the specification fails to teach this medium. As pointed out in the previous Office action and reiterated here, the claims are drawn to a

method of cryopreservation for transfected marrow stromal cells, however, the specification fails to teach a distinct process that would be particularly suitable for BMSCs over other cell types. The specification uses a standard cryopreserving medium and procedure in cryopreservation, the same as *Boswell et al or Zaheer et al* (10% DMSO and 90% medium), therefore, one would not expect any difference among the recovered cells of the cited art and the present application in achieving a level of expression of the exogenous gene of at least about 77% of said predetermined value. The specification and arguments fail to address why using the same cryopreserving medium and procedure the thawed state BMSC of instant invention would be superior to that of the cited prior art of record. The specification fails to provide a distinct new method for cryopreservation of BMSCs, thus, it is applicants' burden to prove that the prior art products do not necessarily or inherently possess characteristics of claimed product, which requires factual evidence demonstrating that actual, unobvious differences exist, and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPBI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ2d 1922, 1923 (BPAI 1989). Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

It is also noted that both *Boswell et al or Zaheer et al* use the same type of medium for preserving hematopoietic cells and stromal cells. Further, *Zaheer et al* clearly teach the motivation for cryopreservation of bone marrows, "CRYOPRESERVED BONE MARROWS ARE WIDELY EMPLOYED IN BONE MARROW TRANSPLANTATION PROCEDURES FOR

HEMATOLOGICAL MALIGNANCIES AND SOLID TUMORS. LONG-TERM STORAGE OF MARROW HAS ALSO BEEN RECOMMENDED FOR WORKERS WITH HIGH RISK OF MARROW APLASIA DUE TO POSSIBLE ACUTE IRRADIATION ACCIDENTS" (1st paragraph of Introduction).

Therefore, it would have been obvious to one of ordinary skill in the art to modify the method taught by *Anderson et al* by simply substituting T lymphocytes or other blood primary cells with BMSCs as taught by *Greenberger et al* and *Boswell et al.* The ordinary skilled artisan would have been motivated to modify the method using BMSCs alone or in combination with hematopoietic cells for an enhanced gene transfer and an enhanced regeneration of bone marrow. The ordinary skilled artisan would have been sufficiently motivated to do so for any types of primary cells, at any stage of the experimentation, i.e. transfecting thawed and recovered cells or transfecting fresh cells and storing the left-over cells for future use, such as taught by *Anderson et al.* Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary. The teaching of *Zaheer et al* does not contradict the combined teachings of foregoing, and provides further insights for the levels of the skilled in the pertinent art at the time before the instant effective filing date, therefore, further supports the view of the Office. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Applicants further argue that even if one were to assume that the Examiner has established a proper basis for a *prima facie* case, applicants submit that the present rejection is based on hindsight. There are at least two lines of evidence demonstrating the nonobviousness of the claims: the absence of intervening art and the solution of a

long felt need; that 5 years after the disclosure of *Greenberger et al*, there is no indication in the publications that a BMSC was cryopreserved such that it retained at least 77% of expression of an exogenous gene; that Zaheer et al published in 1994 still demonstrates the difficulty in effectively cryopreserving BMSCs.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Further, assuming it is a long felt need in the field to develop a new method for cryopreservation of transfected BMSCs, the instant specification fails to disclose such a new method as discussed in the preceding paragraphs.

Therefore, the rejection stands.

Claims 1-10, 21-26, 29, and 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Anderson et al* (US 5 399 346, 3-21-1995), *Greenberger et al* (EP 0 381 490 A2, 8-8-90), and *Boswell et al* (Exp. Hematol 1983), as applied to claims 1-5, 7-10, 21, 22, 24-26, 29, and 30 above, and further in view of *Lozier et al* (Hum Gene Ther 1994) for the reasons of record and following.

Applicants basically reiterated previous argument that *Lozier et al* reference provides no basis to overcome the deficiencies of the combined teachings of *Anderson et al*, *Greenberger et al*, and *Boswell et al,* that *Lozier et al* taught a process comprising the steps of first cryopreserving the BMSCs, then thawing and transducing the cells.

In response, the Loister reference is applied for the teaching of a canine model. Although the more common practice in the art is demonstrated by *Loister et al*, i.e. transforming the BMSCs after thawing, this could be done in a different way as taught by *Anderson et al*, as long as the cells are viable, an exogenous gene could be expressed at a appropriate level meeting the claim limitation, regardless whether they are transformed before or after the cryopreservation. Further, the instant specification fails to provide a distinct process for BMSC cryopresevation, therefore, it is applicants' burden to prove that the prior art products do not necessarily or inherently possess characteristics of claimed product, which requires factual evidence demonstrating that actual, unobvious differences exist, and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPBI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ2d 1922, 1923 (BPAI 1989). Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-5 and 7-11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Anderson et al* (US 5 399 346, 3-21-1995), *Greenberger et al* (EP 0 381 490 A2, 8-8-90), and *Boswell et al* (Exp. Hematol 1983), as applied to claims 1-5

and 7-10 above, and further in view of *Lobb et al* (Biochem Biophy Res Com, 1991), and the rejection applies to claims 21, 22, 24-30 for the reasons of record and following.

Claims 27 and 28 are drawn to the same subject matter of original claims 10 and 11, an exogenous gene encodes a cell surface molecule, particularly VCAM1. Therefore, the same rejection applies to claims 27 and 28.

Applicants argue that *Lobb et al.* discloses the expression of secreted recombinant soluble VCAM-1 in CHO cells followed by purification of the secreted recombinant protein, which lacks a transmembrane region and thus is not a cell surface molecule. Applicants further argue that Lobb et al. does not disclose expression of any cell surface molecule and does not provide any information that overcomes the deficiencies in the other publications.

The arguments have been carefully considered but found not persuasive.

Lobb et al clearly teach that VCAM1 is a cell surface molecule that binds to integrin VLA4 and may help recruit VLA4-expressing leukocytes and eosinophils to inflammatory sites in vivo (1st paragraph, page 1498). For research purpose, *Lobb et al* did synthesize a soluble form of VCAM1 by deleting the transmembrane region. However, they compared the function of the soluble form with that of surface form having the transmembrane region (see the last paragraph, page 1503). The teachings suggest that Lobb et al not only contemplated that VCAM1 is a surface molecule and could be used for leukocyte targeting, they in fact have transfected cells with the full-length VCAM previously.

Again, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, the combined teachings suggest that a skilled artisan knows an adhesion molecule could be used for leukocyte targeting, and the ordinary skilled artisan would have been motivated to modify the claimed invention using an adhesion molecule in targeting BMSCs with a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
September 16, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER